2. (Amended) A nucleic acid molecule comprising:

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a first nucleic acid sequence comprising an aptamer linked via Watson-Crick base pairing to a second nucleic acid sequence comprising a biological effector sequence, wherein the binding of said aptamer to a cell surface molecule permits the internalization by said cell of said nucleic acid sequence comprising a biological effector sequence.

19. (Amended) A method of introducing a biological effector sequence into a cell comprising contacting the molecule of claim 1 or 2 with a host cell, wherein said aptamer of said molecule of claim 1 or 2 binds to a cell surface molecule of said host cell, and permits the internalization of said biological effector sequence, and whereby said biological effector sequence is internalized by said host cell.

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20. (Amended) A method of introducing a biological effector sequence into a cell using the molecule of claim 1 or 2, comprising administering said molecule to an organism comprising said cell, wherein upon binding of the aptamer of said moleucle of cliam 1 or 2 to a molecule on the surface of said cell, said biological effector sequence is internalized by said cell.

21. (Amended) A method of introducing a biological effector sequence into a cell comprising administering to an organism the composition of claim 16, wherein the aptamer of said bifunctional molecule of said composition of claim 16 binds to a molecule on the surface of said cell, and permits the internalization of said biological effector sequence, and wherein the biological effector sequence of said bifunctional molecule of said composition of claim 16 is internalized by said cell.

22. (Amended) A method of introducing a biological effector sequence into an organism, comprising:

introducing a biological effector sequence into a host cell by contacting the molecule of claim 1 or 2 with said host cell, wherein the aptamer of said molecule of claim 1 or 2 binds to a molecule on the surface of said host cell, and permits the internalization of said biological effector sequence, and wherein said biological effector sequence of said molecule of claim 1 or 2 is internalized by said host cell; and administering said host cell to the organism.

Pending claims

Claims 1 to 22 are pending. Claims 1, 2, 19-22 are amended. Upon entry of this Amendment and Response, claims 1-22 are presented for examination. No new matter is added by this amendment. Support for the amended claims is found throughout the specification, and

at least at page 9, lines 17-18 and 21-22, page 24, lines 22-23, and in the claims as originally filed.

The present invention relates to a bifunctional nucleic acid molecule which includes a first nucleic acid sequence comprising an aptamer which is capable of binding to a cell surface molecule, covalently bonded, or hybridized to a second nucleic acid comprising a biological effector sequence, such that binding of the aptamer to a cell surface molecule permits the internalization of the biological effector sequence. The invention also provides methods for introducing a nucleic acid sequence into a cell wherein the cell is contacted with a bifunctional nucleic acid molecule of the invention such that binding of the aptamer portion of the bifunctional nucleic acid molecule to a molecule on the surface of the cell permits the internalization of the biological effector sequence.

Formal Matters

Objection to Claim 21 for Improper Claim Dependency

The Examiner has objected to claim 21 under 37 C.F.R. §1.75(c) as beind of improper dependent form because a multiple dependent claim must refer to the multiple other claims in the alternative only. Applicants submit that claim 21 has been amended, and is now in proper dependent form. Applicants request that the objection be withdrawn.

Rejection of Claims 1-22 Under 35 U.S.C. §101

The Examiner has rejected claims 1-22 under 35 U.S.C. §101 for lacking a specific asserted utility or a well established utility. The Examiner contends that the claims are drawn broadly to nucleic acid molecules comprising a "biological effector sequence" and "methods of performing gene therapy in humans which has not been shown to be an operable and, therefore useful, process". Applicants respectfully disagree with the Examiner.

The "Utility Examination Guidelines" (Federal Register, Vol. 66, No. 4; January 5, 2001) sets forth the guidelines for the examination of patent applications with respect to the utility requirements of 35 U.S.C. §101. The guidelines state that "[I]f at any time...it becomes readily

apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility". An invention has a well-established utility if "a person of ordinary skill in the art would immediately appreciate why the invention is useful...and...the utility is specific substantial and credible". The guidelines further state that if "the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection" (emphasis added).

The claims of the present invention are drawn to nucleic acid molecules comprising a biological effector sequence and methods for introducing the biological effector sequence into a cell. The specification states in the Background section that "methods for the transfer of nucleic acids into cells are of great utility for both physicians and experimental biologists" (page 2, lines 9-10). The specification further states that it is an "object of the invention to provide compositions and methods for introducing nucleic acids...into cells using aptamers as ligands" (page 4, lines 20-21). In addition, the specification, on pages 24-29, contains a description of multiple uses for the present invention, including introducing a biological effector sequence to a cell *in vitro*, *in vivo*, or *ex vivo*. Thus, the specification asserts a specific and substantial utility in that the compositions and methods disclosed therein are useful for introducing a nucleic acid sequence into a host cell. The specification also asserts a credible utility in that the internalization of a nucleic acid sequence is of value to those of skill in both the experimental and clinical scientific arts. Thus, the specification satisfies the legal requirement as set out in 35 U.S.C. §101.

Applicants respectfully remind the Examiner that the invention relates to a method for introducing a nucleic acid molecule into a host cell. While one of skill in the art may use the methods of the present invention for human gene therapy (as asserted by the Examiner above), neither the invention nor the claims are limited as such, and therefore an art-recognized problem of gene therapy operability in humans is not fatal to the asserted utility of the invention: a method for introducing a nucleic acid into a cell.

The Examiner asserts that

> "no specific utility for the claimed invention nucleic acid molecules or methods is disclosed, i.e., delivery of a *specific* biological effector to a *specifc* organism by a *specific* route and which results in or would reasonably have been expected by one of skill in the art to result in a *specific* therapeutic effect is described" (emphasis added)

Applicants submit that they believe that the Examiner is holding the specification to a higher legal standard for the sufficiency of an assertion of a specific utility than that set forth in the Utility Examination Guidelines. The Guidelines state that a claimed invention must have a specific and substantial utility, and this requirement "excludes "throw-away", "insubstantial", or "nonspecific" utilities, such as the use of a complex invention as landfill". Applicants submit that by the standards of the guidelines, the specification asserts a specific utility for the present invention in the assertion that the utility "of the invention [is] to provide compositions and methods for introducing nucleic acids...into cells using aptamers as ligands" (page 4, lines 20-21). Where a claim in a patent application may encompass a genus, there is no requirement in the Guidelines that to assert a specific utility, the specification must assert a *species-specific* utility for each particular species of the invention, as suggested by the Examiner.

In addition, the Examiner asserts that the specific utility assertion must convey to "one of skill in the art [that the invention would] result in a specific **therapeutic** effect" (emphasis added). Applicants respectfully point out that the claims of the present invention do not require a therapeutic effect, but are drawn to nucleic acid molecules and methods for introducing such molecules into a cell. The specification is rife with statements relating to the use of the bifunctional nucleic acid molecules of the present invention for the introduction of a biological effector sequence into a host cell as claimed (see, for example, page 2, line 7; page 4, lines 20-21; pages 24-29; Example 6). Applicants submit that even the title of the present invention "Nucleic acid compositions and **methods of introducing nucleic acids into cells**" makes an assertion of a specific, substantial and credible utility. Applicants respectfully submit further that the therapeutic safety and efficacy of the present invention is not within the purview of the Patent Office. As noted in *Scott v. Finney*, "testing for the full safety and effectiveness of a...devise is more properly left to the Food and Drug Administration...Title 35 does not demand

p. 21 → gene therapy

that such human testing occur within the confines of the Patent and Trademark Office". *Scott v. Finney*, 34 F.3d 1058, 32 USPQ2d 1115 (Fed. Cir. 1994).

Applicants accordingly submit that the specification asserts a specific, substantial, and credible utility as required by the 35 U.S.C. §101, and request that the rejection be reconsidered and withdrawn.

Rejection of Claims 1-22 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-22 under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner states that "since the invention is not supported by either a specific asserted utility or a well established utility...one skilled in the art would not know how to use the claimed invention". Applicants submit that, as expressed above, the specification does, in fact, assert a specific, substantial, and credible utility. The specification clearly asserts that the bifunctional molecules of the invention are useful for introducing a biological effector sequence into a host cell. Accordingly, Applicants submit that the Examiner's rejection of the claims under §112, first paragraph is moot in view of the asserted utility of the present invention. Applicants respectfully request that the rejection be reconsidered and withdrawn.

The Examiner states that a skilled practitioner in the art would have experienced undue experimentation in attempting to practice the claimed invention methods of "introducing a biological effector sequence into a cell" in an organism and "administering said molecule to an organism". In the event that, despite the reasoning set forth in the preceeding paragraph, the Examiner maintains the enablement rejection of methods claims 19-22, Applicants submit the following.

The Examiner states that the specification is "primarily directed to gene therapy of animals including humans", and that the prior art at the time the application was filed taught that gene therapy and antisense therapy were "inoperative at worst and unpredictable at best" (citing Orkin et al., 1995, Report and recommendations...National Institutes of Health). The Examiner cites Orkin et al. as reporting "the low frequency of gene delivery to target cells and the lack of definable biochemical or clinical endpoints", and states that the specification "fails to identify

any biochemical or clinical endpoints". Applicants submit that the claims of the present application relate to methods for introducing a biological effector sequence into a cell comprising either contacting a cell with a bifunctional nucleic acid molecule of the invention which comprises an aptamer, or administering a bifunctional nucleic acid molecule of the invention which comprises an aptamer to an organism which comprises the cell into which the biological effector sequence is to be introduced, whereby, in either scenario, the aptamer binds to a cell surface molecule on the target cell and the biological effector sequence is internalized by the cell. Applicants respectfully submit that a biochemical or clinical endpoint for the claimed methods is irrelevant. While the introduction of a biological effector sequence of the invention into a cell may produce a therapeutically relevant effect, the test for the operability of the *claimed invention* is whether a biological effector sequence is introduced into a cell, not whether the introduction of the sequence into the cell has a therapeutic endpoint. The Examiner also points out that antisense oligonucleotide have been shown to have unexpected effects, such as an increase in cellular activity instead of the anticipated decrease in activity, and unexpected morbidity in some test animals to which the antisense oligonucleotides were administered. Applicants again respectfully submit that this is irrelevant with respect to the present invention. The invention relates to introducing a biological effector sequence into a cell. While it may be that some biological effector sequences have unexpected effects on the cell once internalized has no bearing on whether the present invention is enabled for a method to introduce those sequence into the cell.

In addition, the specification teaches that the claimed methods of the present invention work. Example 6 teaches that antisense sequences which target green fluorescent protein coupled to an aptamer with high affinity for the cell surface receptor L-selectin are capable of inhibiting the expression of GFP, indicating the internalization of the antisense molecule. Although the specification does not teach a working example of introduction of a biological effector molecule *in vivo*, Applicants submit that the specification provides sufficient teaching to permit one of skill in the art to practice the claimed invention without undue experimentation. Applicants submit that the law does not require working examples for every embodiment, or for any embodiment, for that matter. Rather, the law requires that the specification teach one of skill

in the art the necessary steps to determine, without undue experimentation, whether a particular embodiment is functional as claimed. Ex parte Mark, 12 U.S.P.Q.2d 1904 (Bd. Pat. App. & Int. 1989). For the presently claimed invention, the law requires that the specification provide guidance for one of skill in the art to 1) prepare a bifunctional nucleic acid molecule, 2) contact a cell with the bifunctional nucleic acid molecule, and 3) determine whether the biological effector sequence is internalized by the cell. Applicants submit that he specification teaches the following:

1) Pages 9-12 teach the design and production of aptamers useful in the invention;

2) Pages 12-13 teach how to make nucleic acid molecules useful in the invention;

3) Pages 14-17 teach examples of biological effector molecules useful in the invention;

4) Pages 17-18 teach how to assemble a bifunctional nucleic acid molecule;

5) Pages 24-29 teach how to use a bifunctional nucleic acid molecule of the invention to introduce a biological effector sequence into a cell *in vitro, in vivo,* or *ex vivo*;

6) Pages 18-22, and 27-28 teach how to test for the internalization of a biological effector sequence.

Thus, the specification provides ample teaching to guide one of ordinary skill in the art to carry out each of these steps.

Accordingly, applicants submit that the specification is enabling for the full scope of the claimed invention. Applicants therefore request that the rejection be reconsidered and withdrawn.

Rejection of Claims 3-6 and 19-22 Under 35 U.S.C. §112, Second Paragraph

Claims 3-6, and 19-22 have been rejected under 35 U.S.C. §112, second paragraph for indefiniteness. The Examiner states that the phrase "said nucleic acid molecule" in claims 3-6 lacks antecent basis because it is unclear whether the "molecule" is the first, second or third nucleic acid molecule of claims 1-4. Applicants respectfully point out that claims 1-2 recite "a nucleic acid **molecule**" comprising a first, second and third (recited in dependent claim 3)

"nucleic acid **sequence**". Thus the phrase "said nucleic acid molecule" refers to the "**molecule**" recited in the preamble of claims 1 and 2, and not the "**sequence**" recited in the body of the claim. Thus, Applicants submit that the phrase "said nucleic acid molecule" has proper antecedent basis.

The Examiner has rejected claim 10, stating that "claim 10 is confusing because". The reason for the Examiner's confusion is not stated, however. Applicants request clarification of what the Examiner found confusing about claim 10.

The Examiner has rejected claims 19-22 as indefinite for being *non sequitur* to claims 1 or 2 from which they depend. The Examiner suggests that claims 19-22 be amended to indicate "what, if any, relationship the 'aptamer' has to the method of 'introducing'". Applicants have amended claims 19-22 to recite "said aptamer of said molecule of claim 1 or 2 binds to a cell surface molecule of said host cell and permits the internalization of said biological effector sequence". Applicants submit that this amendment makes clear the relationship between the aptamer and the method of introducing the biological effector into a host cell.

The Examiner has rejected claims 19-22 as being indefinite for failing to recite "positive, active method steps" for "introducing...into a cell" because "contacting" and "administering" are not method steps of "introducing...into". The Examiner suggests that Applicants amend the claims to recite positive steps of getting the molecule into the cell and the cell into an organism. Applicants respectfully disagree with the Examiner.

In making the rejection, the Examiner has relied on *Ex parte Erlich*, where the claims at issue were as follows:

> 1. Continuous cell lines producing antibodies specific for human fibroblast interferon which comprise fused cell hybrids derived from human fibroblast interferon primed vertebrate antibody producing cells and cancer cells.
>
> 4. Monoclonal antibodies specific for human fibroblast interferon produced by the continuous cell lines of claim 1.
>
> 6. A process for using monoclonal antibodies of claim 4 to isolate and purify human fibroblast interferon.

7. A process for using monoclonal antibodies of claim 4 to identify human fibroblast interferon.

While the Board of Appeals found that the language of claims 6 and 7 was indefinite, this conclusion was based on the requirement "that a method claim should at least recite a positive, active step(s)." 3 USPQ2d 1017. Review of the claims at issue in *Erlich* shows that claim 4 is simply a composition claim for monoclonal antibodies. Claims 6 and 7, which were rejected, merely set forth a "process for using" monoclonal antibodies. Thus, the claims at issue never recite a positive step, such as "contacting" and "administering" as now set forth in the claims of the present invention.

In an effort to more distinctly and clearly claim the present invention, Applicants have amended claims 19-22 to recite that the aptamer binds to a cell surface molecule, and that the biological effector sequence is internalized by the cell. Applicants submit, however, that claims 19-22 otherwise meet the requirement set forth in *Erlich* for the recitation of "a positive, active step(s)".

The Examiner has rejected claim 20 as being confusing because the relationship between the "cell" and the "organism" is unclear. Applicants submit that claim 20 has been amended to more clearly indicate the relationship between the "cell" and the "organism".

The Examiner has rejected claim 22 for lack of antecedent basis of "an organism". The Examiner suggests that the claim be amended to recite "the organism" to provide direct reference to the antecedent "organism". Applicants have amended claim 22 accordingly.

Applicants submit that the claims as amended are not indefinite, and clearly point out and distinctly claim the present invention. Applicants accordingly request that the rejections be reconsidered and withdrawn.

Rejection of Claims 1, 3, 5, 7, and 16 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 1, 3, 5, 7, and 16 under 35 U.S.C. §102(b) as being anticipated by Gold et al. (U.S. Pat. No. 5,270,163). The Examiner asserts that Gold teaches a nucleic acid molecule comprising an aptamer linked to a nucleic acid sequence comprising a

biological effector sequence, and wherein a third sequence comprising a different aptamer can be linked or hybridized to the nucleic acid molecule. The Examiner also states that Gold teaches a composition comprising the nucleic acid molecule of the present invention in a biologically acceptable carrier. Applicants respectfully disagree with the Examiner.

Applicants submit that Gold teaches a method (the SELEX method) of screening and selecting for nucleic acid molecules which can act as ligands and bind to a target molecule based on their secondary and tertiary structure. Gold also teaches that the nucleic acid sequence of a nucleic acid ligand may be extended to include the sequence of an additional ligand which will bind to a second location on the same target molecule. There is no teaching in Gold, however, of a bifunctional nucleic acid molecule comprising an aptamer and a biological effector sequence.

The present specification teaches that a biological effector sequence is a "nucleic acid that possesses a biological activity" (page 5, lines 4-5), such as sequences which encode useful polypeptides or polynucleotides, sequences that are antisense to nucleic acids that are present in a target cell, nucleic acid enzymes, and nucleic acid sequences that can regulate biochemical processes by cis-acting mechanisms (page 14, lines 2-7). Moreover, the claims of the present invention recite that the binding of the aptamer of a bifunctional nucleic acid molecule to a cell surface permits the internalization of the biological effector sequence.

The nucleic acid molecules taught by Gold do not possess a biological activity. Gold teaches that the nucleic acid molecules taught therein can be used to "bind specifically to a particular target molecule and affect the function of that molecule" (col. 31, lines 14-15). The nucleic acid ligands taught by Gold can only modify the function of the target molecules to which they bind. The nucleic acid ligands taught by Gold merely bind to a molecule. Any modification in the activity of that molecule is a secondary effect, which is not directly induced by the nucleic acid ligand; i.e., binding of the nucleic acid ligand to a protein can interfere with a natural ligand of the protein, or binding of the nucleic acid ligand can sequester small molecules, or the activity of an enzyme can be altered by the binding of a nucleic acid ligand (presumably binding to the active site of the enzyme) (see col, 31, lines 20-30). As taught in col. 9, lines 18-20, the "nucleic acid ligands...bind to a target molecule [and]...modify the function of the target

molecule". Thus, the nucleic acid ligands of Gold modify the function of the molecule to which they are bound. In contrast, the bifunctional nucleic acid molecules of the present invention comprise a portion (aptamer) which binds to a target on the cell surface and a second portion (biological effector) which modifies the function of in intracellular component. Thus, the bifunctional nucleic acid molecules of the present invention modify the function of a different target than the one to which they are bound at the cell surface. Moreover, unlike the present invention, the nucleic acid molecules of Gold do not include a biological effector sequence which possesses a biological activity. Also unlike the present invention, the nucleic acid molecules of Gold are not internalized by a cell.

Applicants therefore submit that Gold does not teach each element of the claimed invention, and therefore does not anticipate the claimed invention. Applicants request that the rejection be reconsidered and withdrawn.

Rejection of Claims 1, 3, 5, 7, 8, 12-14, and 16-18 Under 35 U.S.C. §102(e)

Burke

The Examiner has rejected claims 1, 3, 5, 7, 8, 12-14, and 16-18 under 35 U.S.C. §102(e) as being anticipated by Burke et al. (U.S. Pat. No. 5,637,459) in view of Gold et al. The Examiner asserts that Burke teaches each aspect of the claimed bifunctional nucleic acid molecules of the present invention. Applicants respectfully disagree.

Applicants submit that Burke teaches chimeric nucleic acid molecules which are designed using the same methods as those disclosed in Gold (Gold is a co-inventor on the Burke patent). The chimeric nucleic acid molecules comprise two high affinity binding domains to a single target molecule. Alternatively, Burke teaches that the chimeric nucleic acid molecules may function to assemble a multi-subunit molecule. There is no teaching in Burke of a bifunctional nucleic acid molecule comprising an aptamer and a biological effector sequence, wherein binding of the aptamer to a cell surface molecule permits the internalization of the biological effector sequence. The predominant teachings in Burke relate to the assembly of multi-subunit-type molecules, wherein one portion of a chimeric nucleic acid molecule binds to a

first target and a second portion of the chimeric nucleic acid molecule binds to a second target. Any modification of the function or properties of either of the first or second targets is effected merely by their close spatial proximity resulting from their both being bound by the chimeric nucleic acid molecule (see, for example, the description of acetyl groups from acetyl CoA to chloramphenicol; col. 17, lines 14-25). That is, the components of the chimeric nucleic acid molecule itself do not possess any biological function other than the ability to bind a target molecule.

Burke does teach the assembly of a chimeric nucleic acid molecule comprising a first portion which is a ribozyme which cleaves near the HIV-1 genome site which binds the tat protein (TAR), and a second portion which is an RNA ligand to tat. Thus, binding of the second portion to tat protein brings the ribozyme portion into close proximity to its cleavage site whereby cleavage may occur. The present claims teach a bifunctional nucleic acid molecule comprising a nucleic acid sequence which is an aptamer. The instant specification defines an aptamer as a "nucleic acid molecule that is capable...of binding to a cell surface molecule". The chimeric nucleic acid molecule taught by Burke for the cleavage of the TAR protein does not comprise a nucleic acid sequence which can bind to a cell surface molecule. The only binding function of the particular chimeric molecule taught by Burke is to tat. Tat is not a cell surface molecule. In addition, Burke does not teach that a biological effector sequence is internalized by a cell following binding of an associated aptamer to a cell surface molecule.

Applicants thus submit that the teachings of Burke et al. do not anticipate the present invention. Burke does not teach a bifunctional nucleic acid molecule comprising an aptamer and a biological effector sequence which, upon binding of the aptamer to a cell surface molecule, is internalized by the cell.

Cubicciotti

The Examiner has rejected claims 1, 2, 4, 6, and 7 under 35 U.S.C. §102(e) as being anticipated by Cubicciotti (U.S. Pat. No. 5,656,739). Applicants submit that Cubicciotti teaches bifunctional synthetic heteropolymers comprising a first defined sequence segment capable of specifically binding to a non-oligonucleotide molecule of group of molecules, and a second

defined sequence segment capable of binding to a different non-oligonucleotide moleucle or a selected nucleic acid sequence (col. 3, lines 44-62). Cubicciotti also teaches that the "spatial relationship between the first and second defined sequence segments is optimal to provide for specific binding of the two identified molecules in close intermolecular proximity" (col. 6, lines 5-8). Cubicciotti does not teach a bifunctional molecule comprising an aptamer and a biological effector sequence wherein binding of the aptamer to a cell surface molecule permits internalization of the effector sequence.

Cubicciotti teaches that the bifunctional synthetic heteropolymers described therein can be used to modulate the activity of a molecule bound thereto. However, Cubicciotti teaches that such modulation is mediated by the molecules bound to the heteropolymer, not by the heteropolymer itself. Column 8, lines 22-53 teaches that the

> "binding of a molecule at one defined sequence segment can also modulate the activity of a molecule bound to another defined sequence segment...[A] specifically bound enzyme, for example, may generate any number of products, including hydrogen ions, electrons, photons, heat, substrates, prosthetic groups, cofactors or inhibitors, that can influence the activity of a second bound effector either directly or through effects on the microenvironment"

Thus, no element of the bifunctional synthetic heteropolymers taught by Cubicciotti possess a biological activity. Any biological effect produced according to the methods of Cubicciotti result from the close proximity of the two molecules bound to the heteropolymer, and not from an activity of any portion of the heteropolymer itself. The bifunctional synthetic heteropolymers can not, therefore, be said to comprise a biological effector sequence. In addition, unlike the present invention, there is no teaching in Cubicciotti that the binding of one defined sequence segment of a bifunctional synthetic heteropolymer permits the internalization of a second sequence segment of the same heteropolymer.

Applicants therefore submit that Cubicciotti does not teach each element of the present invention, and thus, does not anticipate the present invention. Applicants therefore request that the rejection be reconsidered and withdrawn.

Rejection of Claims 1-18, and 19-22 Under 35 U.S.C. §103(a)

The Combination of Myers, Toole, Gold, and Burke

Claims 1-18 are rejected under 35 U.S.C. §103(a) as being unpatentable over Myers et al. (WO 88/05077) in view of Toole et al. (WO 92/14843) and in further view of Burke et al. and Gold et al. The Examiner asserts that Myers teaches a nucleic acid molecule comprising a vector comprising a biological effector nucleotide sequence linked to a ligand or "targeting factor" that has cell specific recognition or internalization-promoting properties. The Examiner states that Myers does not teach the use of aptamers as targeting agents for delivering pharmaceuticals to desired targets. The Examiner asserts that it would have been obvious to modify the nucleic acid molecule of Myers with the teachings of Toole to obtain the claimed invention, because one of skill in the art would have been motivated by the obvious advantages of aptamers over proteins, e.g., as taught by Gold: nucleic acids are readily synthesized and amplified, and lack of self-tolerance. The Examiner states that the other elements of the claimed invention are taught by Burke and Gold as described in the rejections under §102. Applicants respectfully disagree.

For the reasons described below, the Examiner has failed to establish a *prima facie* case of obviousness under the requirements of 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Second, there must be a reasonable expectation of success. *Id.* The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. *Id.* Finally, the prior art reference (or references when combined) must teach or suggest *all the claim limitations*. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

There is no motivation to combine Myers and Toole

Applicants submit that while Myers teaches a nucleic acid molecule linked to a "targeting factor" (a factor which promotes or facilitates the penetration of the foreign nucleotides through the cell membrane), and Toole teaches aptamers, there is no motivation to combine these teachings by substituting an aptamer taught by Toole for the protein targeting factor taught by Myers. The Examiner asserts that the motivation to combine Myers and Toole can be found in Gold, in that Gold teaches that nucleic acid ligands are advantageous over protein ligand in their production and use. This does not, however, amount to motivation to substitute the targeting factors of Myers for the aptamers of Toole. There is no teaching in Gold relating to the internalization of a biological effector molecule, and further, there is no teaching in Gold that an aptamer is capable of promoting the internalization of a biological effector sequence to which it is linked or hybridized. Thus, it cannot be said that Gold provides any teachings which would motivate one of skill in the art to substitute a nucleic acid aptamer for the targeting factors of Myers, as there is no teaching in any of the references which would indicate that such substitution would be desirable for purposes of promoting the internalization of a biological effector molecule.

To establish a *prima facie* case of obviousness, the Federal Circuit has stated in *In re Geiger* (815 F.2d 686, 688, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987) that "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching[,] suggestion or incentive supporting the combination." In *Geiger*, the PTO had failed to establish a *prima facie* case of obviousness, and the court went on to say that "[a]t best, in view of these disclosures, one skilled in the art might find it obvious to try various combinations of these known . . . agents. However, that is not the standard of 35 U.S.C. §103." *Id.*, at 1278.

Furthermore, the Federal Circuit has long held that "obvious to try" does not constitute "obviousness." The court in *In re O'Farrell* (853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988)) made an excellent distinction between these two concepts. Judge Rich noted that "[a]ny invention that would in fact have been obvious under §103 would also have been, in a sense,

obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious?" (*Id.* at pages 1680-81). He went on to state that

> The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *[4 case cites omitted]*. In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

(*Id.*, at 1681). The prior art cited by the Examiner clearly falls into Judge Rich's second category. The mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggest the desirability of the particular combination. *Berghauser v. Dann, Comr. Pats.*, 204 U.S.P.Q. 393 (Dist. DC 1979); *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 U.S.P.Q. 929 (Fed. Cir. 1984). Citing references which merely indicate that isolated elements and/or features recited in the claims are known is not a sufficient basis for concluding that the combination of claimed elements would have been obvious. *Ex parte Hiyamizu*, 10 U.S.P.Q.2d 1393 (Bd. Pat. App. & Inter. 1988). The mere statement in Gold of a general advantage of nucleic acid ligands over protein ligands cannot render obvious Applicants' enabled claims to an aptamer linked or hybridized to a biological effector sequence wherein binding of the aptamer to a cell surface molecule permits the internalization of the biological effector. There is no indication in any of the reference, alone or taken together which would indicate the desirability of the substitution suggested by the Examiner, when there is no teaching that such a substitution could even function.

No expectation of success

There are no teachings present in any of the cited references which would have indicated to one of ordinary skill in the art that the protein targeting factors of Myers could be substituted with the aptamers taught by Toole, while still maintaining the internalization of a foreign nucleic acid. Applicants submit that the suggestion in Gold that nucleic acid molecules are

advantageous over proteins as ligands in both their production and ease of use (with respect to immune complications) does not suggest that a nucleic acid ligand can be readily substituted for a protein ligand to achieve the same effect as the protein ligand.

The Combination of Ferkol and Gold

The Examiner has rejected claims 19-22 under 35 U.S.C. §103(a) as being obvious over Ferkol (J. Clin. Invest., 1993) in view of Gold. The Examiner states that Ferkol teaches a method of introducing a biological effector sequence into a human tracheal epithelial cell by contacting such a cell with a biological effector sequence comprising an immunoglobulin fragment specific for a cell surface receptor (pIgR) present on the epithelial cell. Upon binding of the immunoglobulin fragmet to the receptor, the biological effector is internalized. The Examiner states that Gold teaches the use of aptamers as antibodies for *in vivo* applications. The Examiner asserts that it would have been obvious to modify the method of Ferkol with the teachings of Gold (that is, to substitute the immunoglobulin fragment of Ferkol for the aptamer of Gold) given the advantages of aptamers over conventional antibodies in their ease of production and lack of immune complications taught by Gold. Applicants respectfully disagree with the Examiner.

As described above for the Myers, Toole, Gold, Burke combination, Applicants submit that the suggestion in Gold that aptamers are advantageous over antibodies amounts to no more than an invitation to experiment, and does not render the present invention obvious. There are no teachings in either reference which would suggest to an ordinary practitioner that the immunoglobulin fragments of Ferkol could be substituted by aptamers as taught by Gold, while still permitting the internalization of the biological effector sequence. Applicants submit that the Examiner is relying on statements in Gold relating to the general advantages of nucleic acid ligands over antibodies as the sole motivation for substituting aptamers for immunoglobulin fragments. As such, Applicants respectfully submit that, to be equitable, the Patent Office could apply the teachings of Gold in rejections for obviousness of any antibody claims currently pending in the Office. That is, since there is no indication in either reference that substituting an immunoglobulin fragment with an aptamer will result nonetheless in the internalization of a

biological effector sequence, if the suggestion in Gold of advantages of nucleic acid ligands over antibodies is supplies sufficiently a motivation to make such a substitution, then the teachings of Gold might well motivate the same substitution in all inventions relating to antibodies. Applicants thus submit that the teachings of Gold and Ferkol alone, or in combination do not provide adequate motivation for one of skill in the art to have found it obvious to combine their teachings, nor do they suggest that such a combination would be successful.

Accordingly, Applicants submit that the claims of the present invention are not obvious over Ferkol in view of Gold, and request that the rejection be reconsidered and withdrawn.

CONCLUSION

Applicant(s) submit(s) that all claims are allowable as written and respectfully request(s) early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

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